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November 17, 2014

Honorable Paul A. Engelmayer
United States District Judge
Thurgood Marshall United States Courthouse
40 Foley Square
New York, New York 10007

Re: *In re Sanofi Sec. Litig.*, No. 13 Civ. 8806 (PAE); *AG Funds, L.P. v. Sanofi*, No. 14 Civ. 2211 (PAE)

Dear Judge Engelmayer:

We write on behalf of defendants in the above-referenced actions to alert the Court to a development bearing upon defendants' pending motions to dismiss. As disclosed in press releases issued by Genzyme and Sanofi on November 14 and 15, 2014, respectively (copies of which are enclosed), the U.S. Food and Drug Administration (the "FDA") has approved Lemtrada™ based on data from the same rater-blinded Phase 3 clinical studies that formed the basis of Genzyme's original sBLA. A copy of the FDA's approval letter, which was posted to the FDA's website today, is also enclosed.

The Court may take judicial notice of the FDA's approval on the pending motions to dismiss. *See*, *e.g.*, *Simon v. Smith & Nephew, Inc.*, 990 F. Supp. 2d 395, 401 n.2 (S.D.N.Y. 2013) (Engelmayer, J.) ("[T]he Court takes judicial notice of public records contained on the FDA website" on a motion to dismiss); *see also Desabio v. Howmedica Osteonics Corp.*, 817 F. Supp. 2d 197, 201 n.3 (W.D.N.Y. 2011) (same).

We are available at the Court's convenience to answer any questions Your Honor may have.

Respectfully submitted,

/s/ John A. Neuwirth
John A. Neuwirth

cc: By ECF and Email
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Genzyme's Lemtrada Approved by the FDA

Release Date:
Friday, November 14, 2014 9:00 pm EST

Terms:

Dateline City:
CAMBRIDGE, Mass.

- Approval Establishes Genzyme's MS Franchise in the U.S. with Two Approved Products; Follows Global Approvals -

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Genzyme, a Sanofi company, announced today that the U.S. Food and Drug Administration (FDA) has approved Lemtrada™ (alemtuzumab) for the treatment of patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of Lemtrada should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

"*Today's approval is the culmination of more than a decade of work by Genzyme to develop Lemtrada*," said Genzyme President and CEO, David Meeker. *"Lemtrada demonstrated superior efficacy over Rebif on annualized relapse rates in the two studies which were the basis for approval. A comprehensive risk evaluation and mitigation strategy (REMS) will be instituted in order to help detect and manage the serious risks identified with treatment."*

The FDA approval of Lemtrada is based on two pivotal randomized Phase III open-label rater-blinded studies comparing treatment with Lemtrada to Rebif® (high-dose subcutaneous interferon beta-1a) in patients with relapsing remitting MS who were either new to treatment (CARE-MS I) or who had relapsed while on prior therapy (CARE-MS II).

In CARE-MS I, Lemtrada was significantly more effective than interferon beta-1a at reducing annualized relapse rates; the difference observed in slowing disability progression did not reach statistical significance. In CARE-MS II, Lemtrada was significantly more effective than interferon beta-1a at reducing annualized relapse rates, and accumulation of disability was significantly slowed in patients given Lemtrada vs. interferon beta-1a. The clinical development program for Lemtrada involved nearly 1,500 patients with more than 6,400 patient-years of safety follow-up.

"The unmet need in MS remains high," said Edward Fox, M.D., Ph.D., Director of the Multiple Sclerosis Clinic of Central Texas. "*It is a great day for people living with relapsing forms of MS in the United States, who will now have access to this new meaningful treatment".*

The Lemtrada label includes a boxed warning noting a risk of serious, sometimes fatal autoimmune conditions, serious and life-threatening infusion reactions and also noting Lemtrada may cause an increased risk of malignancies including thyroid cancer, melanoma and lymphoproliferative disorders.

Lemtrada is only available through a restricted distribution program, the Lemtrada REMS (Risk Evaluation and Mitigation Strategy). This program has been developed to ensure that access to Lemtrada in the U.S. is only through certified prescribers, healthcare facilities and specialty pharmacies and to also ensure that patients are enrolled in the REMS program. The program is intended to help educate healthcare providers and patients on the serious risks associated with Lemtrada and the appropriate periodic monitoring required to support the detection of these risks for 48 months after the last infusion. The REMS is based on a developmental risk management program that was successfully implemented in the Phase 2 and Phase 3 trials and allowed for early detection and management of some of the serious risks associated with Lemtrada.

"*The FDA approval of Lemtrada is a significant milestone for people living with relapsing MS in the United States*," said Dr. Timothy Coetzee, Chief Advocacy, Services and Research Officer at the National MS Society. "*We are pleased that the voices of the MS community have been recognized and that people with relapsing MS will now have access to a new, needed treatment option*."

Lemtrada has a unique dosing and administration schedule of two annual treatment courses. The first treatment course is administered via intravenous infusion on five consecutive days, and the second course is administered on three consecutive days, 12 months later.

The most common side effects of Lemtrada are rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid gland disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting. Other serious side effects associated with Lemtrada include autoimmune thyroid disease, autoimmune cytopenias, infections and pneumonitis.

First approved in September 2013 in the European Union, Lemtrada is approved in more than 40 countries. Additional marketing applications for Lemtrada are under review by regulatory agencies around the world.

The FDA approval of Lemtrada marks Genzyme's second MS treatment approval in the United States. Genzyme received

FDA approval of its once-daily, oral Aubagio® (teriflunomide) for the treatment of relapsing forms of MS in September 2012. Aubagio is approved in more than 50 countries, and is under review by additional regulatory agencies. Between clinical trials and commercial use, approximately 30,000 patients have been treated with Aubagio.

Multiple sclerosis is estimated to affect more than 2.3 million people globally. There are approximately 400,000 people living with MS in the United States.

Important Safety Information About Lemtrada for U.S. Patients

Serious and life-threatening autoimmune conditions such as immune thrombocytopenia (ITP) and anti-glomerular basement membrane disease can occur in patients receiving Lemtrada. Monitor complete blood counts with differential, serum creatinine levels, and urinalysis with urine cell counts at periodic intervals in patients who receive Lemtrada. Lemtrada is associated with serious and life-threatening infusion reactions. Lemtrada can only be administered in certified healthcare settings that have on-site access to equipment and personnel trained to manage anaphylaxis and serious infusion reactions. Lemtrada may be associated with an increased risk of malignancy, including thyroid cancer, melanoma and lymphoproliferative disorders. The Lemtrada REMS Program, a comprehensive risk management program with frequent monitoring, is being implemented to help mitigate these serious risks.

The Lemtrada label includes a boxed warning noting a risk of serious, sometimes fatal autoimmune conditions, serious and life-threatening infusion reactions and also noting Lemtrada may cause an increased risk of malignancies including thyroid cancer, melanoma and lymphoproliferative disorders. Lemtrada is contraindicated in patients with Human Immunodeficiency Virus (HIV) infection.

U.S. Indication and Usage

Lemtrada is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of Lemtrada should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

Please click here for full U.S. Prescribing Information for Lemtrada, including boxed warning and contraindications.

As part of its continued commitment to MS patients, Genzyme's *MS One to One*® program will provide information about multiple sclerosis, Lemtrada and other relevant resources. *MS One to One* is available and staffed by dedicated MS nurses and highly trained representatives who can provide support for individuals living with MS, their health care providers, family and loved ones. For more information about these support services, call the *MS One to One* line at 1-855-MSOne2One (1-855-676-6326) Monday through Friday, from 8:30am – 8:00pm ET. Information and support are also available at www.MSOnetoOne.com

About Lemtrada™ (alemtuzumab)

Alemtuzumab is a monoclonal antibody that targets CD52, a protein abundant on T and B cells. Circulating T and B cells are thought to be responsible for the damaging inflammatory process in MS. Alemtuzumab depletes circulating T and B lymphocytes after each treatment course. Lymphocyte counts then increase over time with a reconstitution of the lymphocyte population that varies for the different lymphocyte subtypes.

In CARE-MS I, Lemtrada was significantly more effective than interferon beta-1a at reducing annualized relapse rate (0.18 for Lemtrada and 0.39 for interferon beta-1a ($p<0.0001$) a 55 percent relative reduction. The difference observed in proportion of patients with disability progression at year two did not reach statistical significance (8 percent for Lemtrada and 11 percent for interferon beta 1-a ($p=0.22$)), a relative risk reduction of 30 percent. The percent of patients remaining relapse-free at year two for Lemtrada was 78 percent vs. 59 percent for interferon beta-1a ($p<0.0001$). The percent change in T2 lesion volume from baseline did not reach statistical significance (-9.3 for Lemtrada and -6.5 for interferon beta 1-a, $p=0.31$).

In CARE-MS II, Lemtrada was significantly more effective than interferon beta-1a at reducing annualized relapse rates (0.26 for Lemtrada and 0.52 for interferon beta 1-a, $p<0.0001$, a 49 percent relative reduction). The proportion of patients with confirmed six-month disability progression was significantly lower for Lemtrada (13 percent for Lemtrada vs. 21 percent for interferon beta 1-a, $p=0.0084$), a 42 percent relative risk reduction. The percent of patients remaining relapse-free at year two for Lemtrada was 65 percent vs. 47 percent for interferon beta-1a ($p<0.0001$). The percent change in T2 lesion volume from baseline did not reach statistical significance (-1.3 for Lemtrada and -1.2 for interferon beta 1-a, $p=0.14$).

Genzyme holds the worldwide rights to alemtuzumab and has responsibility for its development and commercialization in multiple sclerosis. Bayer Healthcare receives contingent payments based on global sales revenue.

About Aubagio® (teriflunomide)

Aubagio is an immunomodulator with anti-inflammatory properties. Although the exact mechanism of action for Aubagio is not fully understood, it may involve a reduction in the number of activated lymphocytes in the central nervous system (CNS). Aubagio is supported by one of the largest clinical programs of any MS therapy, with more than 5,000 trial participants in 36 countries. Some patients in extension trials have been treated for up to 10 years.

U.S. Indication and Usage

Aubagio (teriflunomide) is a once-daily, oral therapy indicated for the treatment of adult patients with relapsing forms of multiple sclerosis. The recommended dose of Aubagio is 7 mg or 14 mg orally once-daily.

Important Safety Information About Aubagio for U.S. Patients

The Aubagio label includes the risk of hepatotoxicity and, teratogenicity (based on animal data). In the United States, this information can be found in the boxed warning.

In MS clinical studies with Aubagio, the incidence of serious adverse events were similar among Aubagio and placebo-treated patients. Serious events may include decreased white blood cell count, peripheral neuropathy, hyperkalemia, skin reactions and increased blood pressure. The most common adverse events associated with Aubagio in MS patients included increased ALT levels, alopecia, diarrhea, influenza, nausea and paresthesia.

Teriflunomide is the principal active metabolite of leflunomide, which is indicated in the U.S. for the treatment of rheumatoid arthritis. Severe liver injury including fatal liver failure has been reported in patients treated with leflunomide. ALT should be monitored monthly for at least 6 months in patients who start treatment with Aubagio.

Aubagio is contraindicated in patients with severe hepatic impairment, pregnant women and women of childbearing potential who are not using reliable contraception and in patients who are taking leflunomide. Aubagio is not recommended for breast-feeding women, patients with immunodeficiency states, patients with significantly impaired bone marrow function or significant anemia, leucopenia, neutropenia or thrombocytopenia, patients with severe active infection until resolution, patients with severe renal impairment undergoing dialysis and patients with hypoproteinaemia.

Please click here for full U.S. Prescribing Information for Aubagio, including boxed warning and contraindications.

About Genzyme, a Sanofi Company

Genzyme has pioneered the development and delivery of transformative therapies for patients affected by rare and debilitating diseases for over 30 years. We accomplish our goals through world-class research and with the compassion and commitment of our employees. With a focus on rare diseases and multiple sclerosis, we are dedicated to making a positive impact on the lives of the patients and families we serve. That goal guides and inspires us every day. Genzyme's portfolio of transformative therapies, which are marketed in countries around the world, represents groundbreaking and life-saving advances in medicine. As a Sanofi company, Genzyme benefits from the reach and resources of one of the world's largest pharmaceutical companies, with a shared commitment to improving the lives of patients. Learn more at www.genzyme.com.

About Sanofi

Sanofi, a global healthcare leader, discovers, develops and distributes therapeutic solutions focused on patients' needs. Sanofi has core strengths in the field of healthcare with seven growth platforms: diabetes solutions, human vaccines, innovative drugs, consumer healthcare, emerging markets, animal health and the new Genzyme. Sanofi is listed in Paris (EURONEXT: SAN) and in New York (NYSE: SNY).

Sanofi Forward Looking Statements

This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements are statements that are not historical facts. These statements include projections and estimates and their underlying assumptions, statements regarding plans, objectives, intentions and expectations with respect to future financial results, events, operations, services, product development and potential, and statements regarding future performance. Forward-looking statements are generally identified by the words "expects", "anticipates", "believes", "intends", "estimates", "plans" and similar expressions. Although Sanofi's management believes that the expectations reflected in such forward-looking statements are reasonable, investors are cautioned that forward-looking information and statements are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of Sanofi, that could cause actual results and developments to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include among other things, the uncertainties inherent in research and development, future clinical data and analysis, including post marketing, decisions by regulatory authorities, such as the FDA or the EMA, regarding whether and when to approve any drug, device or biological application that may be filed for any such product candidates as well as their decisions regarding labelling and other matters that could affect the availability or commercial potential of such product candidates, the absence of guarantee that the product candidates if approved will be commercially successful, the future approval and commercial success of therapeutic alternatives, the Group's ability to benefit from external growth opportunities, trends in exchange rates and prevailing interest rates, the impact of cost containment policies and subsequent changes thereto, the average number of shares outstanding as well as those discussed or identified in the public filings with the SEC and the AMF made by Sanofi, including those listed under "Risk Factors" and "Cautionary Statement Regarding Forward-Looking Statements" in Sanofi's annual report on Form 20-F for the year ended December 31, 2013. Other than as required by applicable law, Sanofi does not undertake any obligation to update or revise any forward-looking information or statements.

Language:
English

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PRESS RELEASE

Genzyme's Lemtrada Approved by the FDA

- Approval Establishes Genzyme's MS Franchise in the U.S. with Two Approved Products; Follows Global Approvals -

Paris - November 15, 2014 - Sanofi and its subsidiary Genzyme announced today that the U.S. Food and Drug Administration (FDA) has approved Lemtrada™ (alemtuzumab) for the treatment of patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of Lemtrada should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

"*Today's approval is the culmination of more than a decade of work by Genzyme to develop Lemtrada*," said Genzyme President and CEO, David Meeker. *"Lemtrada demonstrated superior efficacy over Rebif on annualized relapse rates in the two studies which were the basis for approval. A comprehensive risk evaluation and mitigation strategy (REMS) will be instituted in order to help detect and manage the serious risks identified with treatment."*

The FDA approval of Lemtrada is based on two pivotal randomized Phase III open-label rater-blinded studies comparing treatment with Lemtrada to Rebif® (high-dose subcutaneous interferon beta-1a) in patients with relapsing remitting MS who were either new to treatment (CARE-MS I) or who had relapsed while on prior therapy (CARE-MS II).

In CARE-MS I, Lemtrada was significantly more effective than interferon beta-1a at reducing annualized relapse rates; the difference observed in slowing disability progression did not reach statistical significance. In CARE-MS II, Lemtrada was significantly more effective than interferon beta-1a at reducing annualized relapse rates, and accumulation of disability was significantly slowed in patients given Lemtrada vs. interferon beta-1a. The clinical development program for Lemtrada involved nearly 1,500 patients with more than 6,400 patient-years of safety follow-up.

"The unmet need in MS remains high," said Edward Fox, M.D., Ph.D., Director of the Multiple Sclerosis Clinic of Central Texas. "*It is a great day for people living with relapsing forms of MS in the United States, who will now have access to this new meaningful treatment".*

The Lemtrada label includes a boxed warning noting a risk of serious, sometimes fatal autoimmune conditions, serious and life-threatening infusion reactions and also noting Lemtrada may cause an increased risk of malignancies including thyroid cancer, melanoma and lymphoproliferative disorders.

Lemtrada is only available through a restricted distribution program, the Lemtrada REMS (Risk Evaluation and Mitigation Strategy). This program has been developed to ensure that access to Lemtrada in the U.S. is only through certified prescribers, healthcare facilities and specialty pharmacies and to also ensure that patients are enrolled in the REMS program. The program is intended to help educate healthcare providers and patients on the serious risks associated with Lemtrada and the appropriate periodic monitoring required to support the detection of these risks for 48 months after the last infusion. The REMS is based on a developmental risk management program that was successfully implemented in the Phase 2 and Phase 3 trials and allowed for early detection and management of some of the serious risks associated with Lemtrada.

"*The FDA approval of Lemtrada is a significant milestone for people living with relapsing MS in the United States*," said Dr. Timothy Coetzee, Chief Advocacy, Services and Research Officer at the National MS Society. "*We are pleased that the voices of the MS community have been recognized and that people with relapsing MS will now have access to a new, needed treatment option*."

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First approved in September 2013 in the European Union, Lemtrada is approved in more than 40 countries. Additional marketing applications for Lemtrada are under review by regulatory agencies around the world.

The FDA approval of Lemtrada marks Genzyme's second MS treatment approval in the United States. Genzyme received FDA approval of its once-daily, oral Aubagio® (teriflunomide) for the treatment of relapsing forms of MS in September 2012. Aubagio is approved in more than 50 countries, and is under review by additional regulatory agencies. Between clinical trials and commercial use, approximately 30,000 patients have been treated with Aubagio.

Multiple sclerosis is estimated to affect more than 2.3 million people globally. There are approximately 400,000 people living with MS in the United States.

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Teriflunomide is the principal active metabolite of leflunomide, which is indicated in the U.S. for the treatment of rheumatoid arthritis. Severe liver injury including fatal liver failure has been reported in patients treated with leflunomide. ALT should be monitored monthly for at least 6 months in patients who start treatment with Aubagio.

Aubagio is contraindicated in patients with severe hepatic impairment, pregnant women and women of childbearing potential who are not using reliable contraception and in patients who are taking leflunomide. Aubagio is not recommended for breast-feeding women, patients with immunodeficiency states, patients with significantly impaired bone marrow function or significant anemia, leucopenia, neutropenia or thrombocytopenia, patients with severe active infection until resolution, patients with severe renal impairment undergoing dialysis and patients with hypoproteinaemia.

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About Sanofi

Sanofi, a global healthcare leader, discovers, develops and distributes therapeutic solutions focused on patients' needs. Sanofi has core strengths in the field of healthcare with seven growth platforms: diabetes solutions, human vaccines, innovative drugs, consumer healthcare, emerging markets, animal health and the new Genzyme. Sanofi is listed in Paris (EURONEXT: SAN) and in New York (NYSE: SNY).

Sanofi Forward Looking Statements

This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements are statements that are not historical facts. These statements include projections and estimates and their underlying assumptions, statements regarding plans, objectives, intentions and expectations with respect to future financial results, events, operations, services, product development and potential, and statements regarding future performance. Forward-looking statements are generally identified by the words "expects", "anticipates", "believes", "intends", "estimates", "plans" and similar expressions. Although Sanofi's management believes that the expectations reflected in such forward-looking statements are reasonable, investors are cautioned that forward-looking information and statements are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of Sanofi, that could cause actual results and developments to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include among other things, the uncertainties inherent in research and development, future clinical data and analysis, including post marketing, decisions by regulatory authorities, such as the FDA or the EMA, regarding whether and when to approve any drug, device or biological application that may be filed for any such product candidates as well as their decisions regarding labelling and other matters that could affect the availability or commercial potential of such product candidates, the absence of guarantee that the product

candidates if approved will be commercially successful, the future approval and commercial success of therapeutic alternatives, the Group's ability to benefit from external growth opportunities, trends in exchange rates and prevailing interest rates, the impact of cost containment policies and subsequent changes thereto, the average number of shares outstanding as well as those discussed or identified in the public filings with the SEC and the AMF made by Sanofi, including those listed under "Risk Factors" and "Cautionary Statement Regarding Forward-Looking Statements" in Sanofi's annual report on Form 20-F for the year ended December 31, 2013. Other than as required by applicable law, Sanofi does not undertake any obligation to update or revise any forward-looking information or statements.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 103948/5139

SUPPLEMENT APPROVAL

Genzyme Corporation
Attention: Jennifer Panagoulias, RAC
Global Therapeutic Head, Regulatory Affairs Neurology
500 Kendall Square
Cambridge, MA 02142

Dear Ms. Panagoulias:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received November 27, 2012, submitted under section 351 of the Public Health Service Act for Lemtrada (alemtuzumab) injection.

We acknowledge receipt of your amendments dated April 15, 2014, May 15, 2014, May 20, 2014, June 13, 2014, July 1, 2014, July 2, 2014, July 10, 2014 (2), July 15, 2014, July 18, 2014, July 21, 2014, July 22, 2014, July 23, 2014, July 29, 2014, July 30, 2014, August 4, 2014, August 6, 2014, August 7, 2014, August 8, 2014, August 27, 2014, September 5, 2014, September 8, 2014, September 12, 2014, October 15, 2014, October 21, 2014, October 27, 2014, November 7, 2014, November 12, 2014, November 13, 2014, and November 14, 2014 (3).

The April 15, 2014, and May 15, 2014, submissions constituted a complete response to our December 27, 2013, action letter.

This Prior Approval supplemental biologics application provides a new indication, the use of Lemtrada for the treatment of patients with relapsing forms of multiple sclerosis, and an associated risk evaluation and mitigation strategy (REMS).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on October 15, 2014, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "Product Correspondence – Final Printed Carton and Container Labels for approved BLA 103948/5139." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because there is evidence strongly suggesting that the drug product would be unsafe in all pediatric age groups. The evidence includes the known risks of serious autoimmune conditions, malignancies, and infections for which patients may be at risk for several years after the last infusion, as well as the risk of potentially fatal infusion reactions.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of embryolethality or to identify the unexpected serious risk of adverse maternal, fetal, and infant outcomes in women exposed to Lemtrada (alemtuzumab) during pregnancy, and of adverse effects on postnatal growth and development in exposed fetuses. In addition, analysis of spontaneous postmarketing adverse events will not be sufficient to assess the known serious risks of autoimmune conditions, malignancies, serious infections including opportunistic infections, and pneumonitis that may occur after a currently undefined period of time following completion of therapy with Lemtrada (alemtuzumab), or the known serious risk of infusion reactions (including anaphylaxis and cardiac and respiratory emergencies) that occur during or after Lemtrada (alemtuzumab) infusion.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2832-1 A prospective, registry-based observational exposure cohort study conducted in the United States, that compares the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to Lemtrada (alemtuzumab) during pregnancy to unexposed control populations (one with women with multiple sclerosis who have not been exposed to Lemtrada (alemtuzumab) in pregnancy and the other in women without multiple sclerosis). The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you submitted on November 12, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/15
Study Completion:	06/20
1st Annual Interim Report:	11/15
2nd Annual Interim Report:	11/16
3rd Annual Interim Report:	11/17
4th Annual Interim Report:	11/18
5th Annual Interim Report:	11/19
Final Report Submission:	04/21

2832-2 A pre- and postnatal development (including maternal function) study of Lemtrada (alemtuzumab) in rHu CD52 mouse.

The timetable you submitted on November 12, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/15
Study Completion:	03/16
Final Report Submission:	09/16

2832-3 A prospective observational registry study in adult patients with relapsing multiple sclerosis, with the primary objective of determining the necessary duration of monitoring following treatment with Lemtrada (alemtuzumab) for multiple sclerosis and to further inform appropriate monitoring conditions. Events of interest include autoimmune-mediated conditions, malignancies, serious infections including opportunistic infections, and pneumonitis. A minimum of 5000 multiple sclerosis patients treated with Lemtrada (alemtuzumab) should be enrolled and followed for a minimum of 10 years following the first exposure to Lemtrada (alemtuzumab). The protocol should specify an appropriate comparator population(s) to which observed incidence rates will be compared.

The timetable you submitted on November 12, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/15
Study Completion:	08/28
1st Annual Interim Report:	11/15
2nd Annual Interim Report:	11/16
3rd Annual Interim Report:	11/17
4th Annual Interim Report:	11/18
5th Annual Interim Report:	11/19
6th Annual Interim Report:	11/20
7th Annual Interim Report:	11/21
8th Annual Interim Report:	11/22
9th Annual Interim Report:	11/23
10h Annual Interim Report:	11/24
11th Annual Interim Report:	11/25
12th Annual Interim Report:	11/26
13th Annual Interim Report:	11/27
Final Report Submission:	03/29

2832-4 A prospective study in adult patients with relapsing multiple sclerosis to assess patient safety during and after Lemtrada (alemtuzumab) infusion in multiple sclerosis patients. Measurements of interest include: 1) Duration of infusion; 2) Vital signs at baseline, during infusion, and during post-infusion observation for each infusion in the infusion cycle; 3) Serious adverse events that occur during and start within 24 hours of infusion; and 4) Serious adverse events that start within 7 days of infusion. A minimum of 300 multiple sclerosis patients treated with Lemtrada (alemtuzumab) should be enrolled.

The timetable you submitted on November 12, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/15
Study Completion:	01/17
Final Report Submission:	07/17

The final protocols for these PMRs should reflect Agency agreement and be submitted prior to starting the studies.

REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)

Submit the protocol(s) to your IND 010717, with a cross-reference letter to this BLA. Submit all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required**

Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)".

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Lemtrada (alemtuzumab) to ensure the benefits of the drug outweigh the risks of autoimmune conditions, infusion reactions, and malignancies.

We have also determined that a communication plan is necessary to support implementation of the REMS.

Pursuant to 505-1(f)(1), we have also determined that Lemtrada (alemtuzumab) can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risks of autoimmune conditions, infusion reactions, and malignancies that are listed in the labeling. The elements to assure safe use will ensure that only certified prescribers prescribe Lemtrada (alemtuzumab), ensure that Lemtrada (alemtuzumab) is dispensed only in certain healthcare settings, specifically, certified pharmacies, and certified infusion sites that have on-site access to equipment and personnel trained to manage infusion reactions; that certified infusion sites monitor patients for infusion reactions during and after each Lemtrada (alemtuzumab) infusion; that only enrolled and authorized patients receive Lemtrada (alemtuzumab); and that certified prescribers submit documentation of periodic monitoring of patients who receive Lemtrada (alemtuzumab) to identify autoimmune conditions and malignancies.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval

of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, submitted on November 14, 2014, and appended to this letter, is approved. The REMS consists of a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Lemtrada into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following:

1. REMS Program Outreach/Communication Plan activities: Genzyme will provide the following:

    a. Numbers of REMS letters sent to prescribers. Include information on initial and follow up mailings via regular mail or email, and the number of mailings that were returned (regular mail) or unopened (email) as well as those that were sent hard copy letters following failure to open second email.

    b. Number of unique visits to the Lemtrada REMS website

2. REMS Program Utilization Statistics

    a. Prescriber certification: for the current reporting period and cumulatively
        i. Number, specialty, and geographic location of newly certified prescribers
            1. Breakdown of number of attempts at knowledge assessment prior to successful completion
            2. Most frequently missed knowledge assessment questions
        ii. Total number of active certified prescribers (i.e., have prescribed the drug during the reporting period for at least 1 patient)
        iii. Number of prescribers deactivated and reasons for deactivation
            1. Number of these that subsequently become re-certified

    b. Patient enrollment: for the current reporting period and cumulatively
        i. Number of newly enrolled patients
        ii. Total number of patients

    c. Certified Infusion sites: for the current reporting period and cumulatively:
        i. Number, geographical location, and site affiliation (academic or community medical center, or other) of newly certified healthcare facilities
        ii. Total number of active certified healthcare facilities (i.e., have administered Lemtrada at least once during the reporting period)
        iii. Number of certified healthcare facilities deactivated and reason for deactivation

d. Certified pharmacies: for the current reporting period and cumulatively:
    i. Number and geographical location of newly certified pharmacies
    ii. Total number of active certified pharmacies (i.e., have dispensed Lemtrada at least once during the reporting period)
    iii. Number of certified pharmacies deactivated and reason for deactivation

e. Dispensing activity: for the current reporting period and cumulatively
    i. Number of orders received and number of orders shipped
    ii. Total number of vials distributed
        1. Number distributed by distributors
        2. Number distributed by certified pharmacies
    iii. Number of vials returned outside of 50 day window
    iv. Disposition of vials once returned (retained or destroyed)

3. REMS Program Infrastructure and Performance

a. Time between receipt of initial Prescription Ordering and Authorization Form and Lemtrada administration (mean, median, range) and an analysis summarizing any reasons for delays

b. Summary of call center data frequently asked questions

c. Unintended system interruptions and resolution

d. Program compliance
    i. Prescribers
        1. Number of non-certified prescribers who have written one or more prescriptions
    ii. Pharmacies
        1. Number of orders shipped to non-certified healthcare facilities
    iii. Distributors
        1. Number of orders shipped to non-certified healthcare facilities
    iv. Infusion centers
        1. Number of administrations occurring in non-certified infusion centers
        2. Number of administrations occurring in non-verified patients
        3. Number of infusion checklists submitted
        4. Number of infusion checklists expected
        5. Number of days between last infusion and receipt of infusion checklist (median, mean, range)
    v. Patient status forms - see proposed table for provision of data*

e. Audit findings
    i. A summary of audit activities to ensure all processes and procedures are in place and functioning to support the requirements of the LEMTRADA REMS Program

ii. Reports of critical observations identified and the associated corrective and preventive action (CAPA) plans, and whether the CAPA plans were satisfactorily completed

4. Evaluation of knowledge – first submission with the 12 month assessment and each annual assessment thereafter

   a. An evaluation of patient understanding of the serious risks of autoimmune conditions, infusion reactions, and malignancies associated with treatment with Lemtrada, and the need for baseline and periodic monitoring

   b. An evaluation of healthcare providers understanding of the serious risks of autoimmune conditions, infusion reactions, and malignancies associated with Lemtrada, the need to counsel patients regarding these risks and the need for baseline and periodic monitoring

   c. An evaluation of healthcare facility staff understanding of the risks of infusion reactions associated with Lemtrada administration and the management and documentation of these reactions, as well as the requirements of the Lemtrada REMS including pre-infusion counseling prior to each infusion.

5. The requirements for assessments of an approved REMS under section 505-1(g)(3) include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

*Compliance with patient status forms

Number received reporting period		Number received program-to-date	Number Expected reporting period	Number Expected program-to-date	% compliance reporting period	% compliance cumulative
stating "no" labs completed						
# no longer under MD care						
without new MD identified						

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

BLA 103948 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

BLA 103948 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 103948
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 103948
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

POSTMARKETING SURVEILLANCE

We request that you provide expedited reporting of the following postmarketing adverse events when they are serious: immune thrombocytopenia, other cytopenias or bleeding events, glomerular nephropathies, herpes viral infections, and opportunistic infections. Annual reporting should include a cumulative analysis of these events.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Hamet Touré, Regulatory Project Manager, at (301) 796-7534.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H Dunn
11/14/2014